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β-blockers or calcium antagonists in silent ischaemia?

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Unrecognized or silent myocardial ischaemia during daily life has generated considerable recent interest as it occurs in all forms of coronary artery disease, ranging from those who are totally asymptomatic to those who have had a myocardial infarction. A characteristic diurnal cycle of both frequency and duration of these ischaemic episodes occurs and is the same as the diurnal variation observed in frequency of acute myocardial infarction and out-of-hospital sudden death. These findings suggest common underlying triggering mechanisms which may couple transient ischaemia to these morbid events. The presence of daily-life silent ischaemia is associated with a two- to five-fold increase in risk of death and similar increases in risk of non-fatal infarction. Multivariate analysis suggests that silent ischaemia is the best independent predictor of outcome (e.g. death, or myocardial infarction) among a number of factors that include coronary angiography and exercise test results.

Anti-anginal agents (e.g. nitrates, β-blockers, calcium antagonists) also reduce or prevent daily-life silent ischaemia. While anti-anginal treatment can control both symptomatic and silent ischaemic episodes, therapy directed towards symptom control alone may be insufficient to control recurrent silent ischaemia in many individuals. A recent report suggests that suppression of painless ischaemia by anti-ischaemic treatment is associated with a reduced risk of adverse outcome.

Additional advances in this area will require the results of large, well-controlled multicentre clinical trials, several of which are currently in progress. We anxiously await the results of these important trials: the Total Ischaemic Burden European Trial (TIBET), the Atenolol Silent Ischaemia Trial (ASIST) and the Asymptomatic Cardiac Ischaemia Pilot (ACIP).

Introduction

The topic of silent myocardial ischaemia has received considerable attention over the past few years for a number of reasons including its high prevalence rate, association with adverse outcome, and controversy about whether or not it should be treated. The purpose of this paper is to place silent ischaemia in perspective relative to its medical treatment. Terminology and pathophysiology will be addressed, as well as pathophysiological mechanisms. Discussion of the latter might help in the selection of a rational approach to pharmacological management of this syndrome, and the relative merits of β-blockers vs calcium antagonists are considered.

TERMINOLOGY

Silent ischaemia may mean different things to different people. Silent ischaemia has been used to describe the totally asymptomatic individual with coronary artery disease (CAD); this could be the patient who has never had symptoms, or the patient who is asymptomatic after myocardial infarction, but has an abnormal exercise ECG or thallium test indicative of transient ischaemia (Table 1). The term is also used when referring to transient asymptomatic left ventricular dysfunction, identified by wall motion abnormalities detected during non-invasive or invasive imaging. Silent ischaemia may also be used to describe the asymptomatic patient with severe coronary artery obstruction at angiography or at post-mortem. The patient who has suffered a silent or unrecognized myocardial infarction is also said to have had silent ischaemia. More commonly silent ischaemia is used to describe the patient with known CAD, with or without symptoms, who also has transient asymptomatic ischaemic type ST segment depression discovered during continuously recorded ECG (either in hospital, usually in the cardiac care unit or during daily life by ambulatory ECG recording). This paper focuses specifically on patients with 'daily-life ischaemia'. Daily-life ischaemia is defined as a period when ischaemic-type ST segment changes occur during the activities of daily life, between 70% and 90% of which are not accompanied by recognizable symptoms. The term daily-life ischaemia is preferable to silent ischaemia, as it avoids confusion with the other situations outlined above and correctly describes a situation that also includes a few symptomatic ischaemic episodes.

Table 1 Silent myocardial ischaemia terminology

Asymptomatic coronary artery disease
Latent coronary artery disease
Silent or unrecognized myocardial infarction
Transient asymptomatic ischaemic-type
electrocardiographic ST-segment depression
abnormal thallium test
left ventricular wall motion abnormalities
myocardial metabolic abnormalities

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Table 2 Considerations to justify treatment of patients with daily-life ischaemia

Proven
Independent risk factor for adverse outcome
Treatment prevents or reduces daily-life ischaemia
Under investigation
Treatment prevents or reduces adverse outcome
Prevention or reduction of ischaemia is associated with reduced risk for adverse outcome compared with those in whom treatment fails to prevent or reduce ischaemia
Reduction in adverse outcome afforded by treatment is cost-effective

WHAT IS THE RATIONALE FOR TREATMENT?

A number of issues provide partial justification for treatment of the largely asymptomatic problem of daily-life ischaemia (Table 2). Daily-life ischaemia is an independent risk factor for adverse outcome of CAD; over 1200 patients studied by ambulatory ECG monitoring and followed for months or years have yielded sufficient data to support this[1,2]. Pharmacological treatment can prevent or reduce daily-life ischaemia; numerous studies (some of which are reviewed in this paper) provide supporting evidence for this. Other issues also important in the justification of treatment of daily-life ischaemia are under investigation. These include questions such as whether the treatment of patients with daily-life ischaemia reduces adverse outcome, or whether prevention or reduction of daily-life ischaemia is associated with a reduced risk for adverse outcome compared with situations where treatment fails to prevent or reduce ischaemia. Finally, it remains to be proved that reduction in adverse outcome in patients, who are not necessarily severely symptomatic, is afforded by a detection strategy and treatment that is cost-effective. When all of these considerations are satisfactorily addressed, treatment of daily-life ischaemia may be justified.

Is daily-life ischaemia a risk factor for adverse outcome?

The studies that deal with daily-life ischaemia and risk of cardiovascular events in patients with stable angina or stable CAD have been reviewed in detail elsewhere[2]. More than 600 patients with stable angina have been studied; the risk ratios for death and adverse outcome (death or non-fatal infarction) are markedly increased in the presence of daily-life ischaemia. In some reports, the risk ratios are approximately four or higher for death or adverse outcome[3–9]; the risk ratio for adverse outcome in a study by Rocco *et al.*[5], for example, reached approximately 14. Data from over 500 patients with unstable angina[10–15], and over 200 post-myocardial infarction patients have also been reported[16,17]. All of these patient subsets behave similarly with respect to the additional importance of daily-life ischaemia, except that the risk ratios for adverse outcome appear somewhat higher for unstable angina and postinfarction patients than for patients with stable CAD syndromes. Several studies also used multivariate analysis and concluded that daily-life ischaemia was the most important independent predictor of adverse outcome[5,9,18].

Thus, there are ample data to conclude that daily-life ischaemia is an independent risk factor for adverse outcome in these patient populations.

Does anti-anginal therapy control daily-life ischaemia?

Does anti-anginal therapy in the usual clinical setting also control daily-life ischaemia? Mulcahy and co-workers[19] reported that in 114 patients with stable angina pectoris who were receiving what was thought to be clinically optimal anti-anginal therapy, about one-third continued to have ischaemic episodes during daily monitoring. Data from other studies support this conclusion, and suggest that about 40% of patients who are thought to be effectively treated for suppression of angina, continue to have daily-life ischaemia[9]. Deedwania and colleagues[9] found that treated patients who continued to have daily-life ischaemia had reduced survival compared with those who did not. Recently, Yeung and co-workers[20] confirmed this suggestion. It can be concluded, therefore, that symptom-titrated anti-anginal therapy does not prevent daily-life ischaemia in a significant minority of patients.

Pathophysiological clues to appropriate pharmacotherapy

Some suggest that most silent ischaemia is not necessarily due to physical activity and that environmental and mental stress may play an important role[21,22]. These conclusions were based on detailed diary analysis. Others found that the heart rate at onset of most daily-life ischaemia was lower than the heart rate observed in the same patients at onset of ischaemia induced in the treadmill laboratory. In another study, ambulatory monitoring over 3 consecutive days[23] showed that both heart rate and ischaemic activity oscillate in diurnal patterns characteristic of the patterns for both myocardial infarction and out-of-hospital sudden death (Fig. 1). Heart rate begins to increase shortly after waking, is fastest about noon, and is slowest during sleep. Ischaemic activity occurs frequently during periods when the heart rate is increased, and infrequently when the heart rate is slowed. β-blockade eliminates the oscillations in heart rate and markedly reduces ischaemic activity. In addition, the residual ischaemic activity that occurs during β_1-adrenergic blockade does not have a circadian pattern. These observations suggest that ischaemic activity occurring during daily life is very closely coupled to the oscillations in heart rate that occur during the day, and that this diurnal variation in heart rate is mediated, in part, by β_1-adrenergic activation.

Recently, Deedwania and Nelson[24] recorded the ambulatory ECG and ambulatory blood pressure throughout a 24-hour period in a group of CAD patients (Fig. 2). Heart rate and ischaemia patterns were similar to those described by other laboratories[23]. Increases in heart rate, systolic blood pressure and ischaemic activity occur in the early morning hours shortly after the patient wakes and becomes active. Although not measured directly, contractility

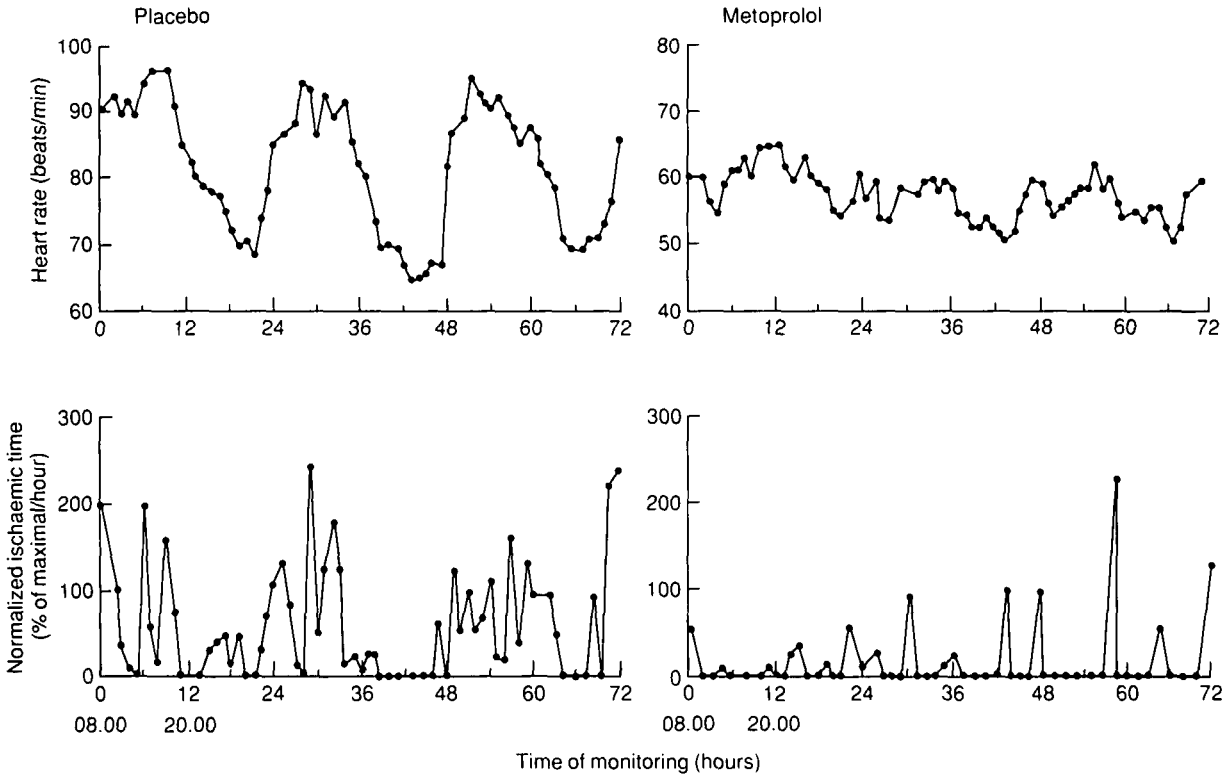

Figure 1 Daily variation in heart rate and ischaemia during treatment with placebo or metoprolol. From Lambert and Pepine[23].

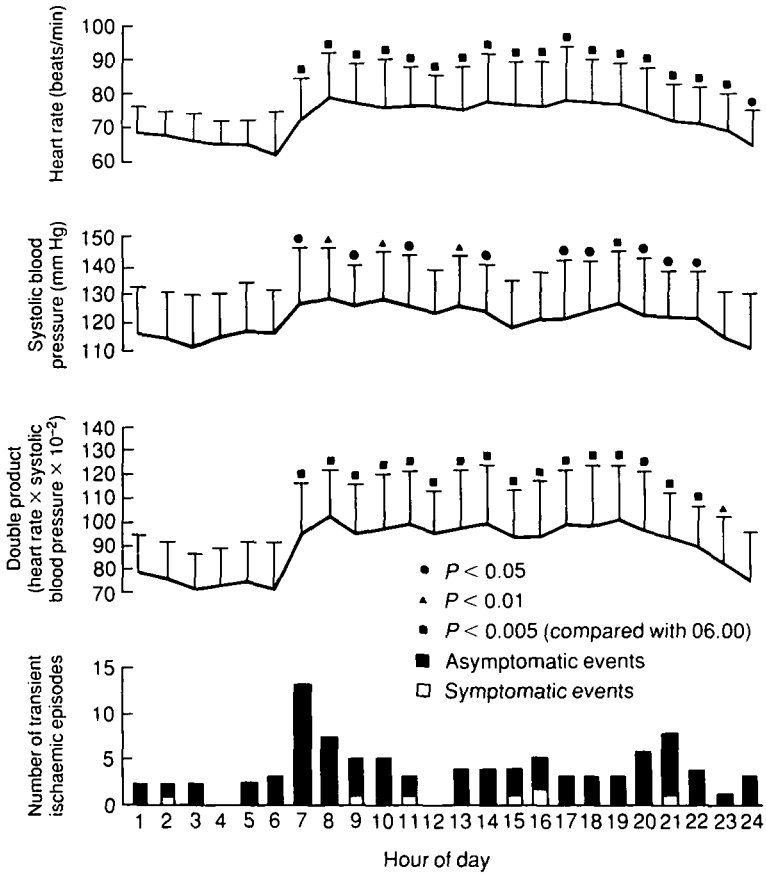

Figure 2 Circadian pattern of transient ischaemic episodes, heart rate, systolic blood pressure and double product. From Deedwania and Nelson[24].

probably also increases during these hours of β_1-adrenergic activation. It seems reasonable to conclude that increases in myocardial oxygen demand are, at least in part, responsible for ischaemic episodes that occur during daily life, but as neither the heart rate nor blood pressure increases recorded during daily life reach the levels achieved at the onset of ischaemia during treadmill exercise, other factors must also be involved. These include an increase in myocardial oxygen demand which is not reflected in the heart rate and systolic blood pressure, or in a reduction in myocardial oxygen delivery. Recent evidence indicates that cold exposure and mental stress (which are known to increase indices of myocardial oxygen demand) also provoke coronary artery constriction at sites of endothelial dysfunction[25,26]. This suggests that environmental stresses may function as important triggers for daily-life ischaemia by limiting coronary blood flow in the setting of increased myocardial oxygen requirements.

One or several of these factors will determine the mechanism (in terms of increased myocardial oxygen demand and reduced supply) responsible for an individual ischaemic episode and the mechanisms are likely to vary from patient to patient and ischaemic episode to ischaemic episode. Clearly, increases in heart rate and β_1-adrenergic activation are very important.

Calcium antagonist or β-blocker for daily-life ischaemia?

β-BLOCKERS

A large amount of data has been published from controlled trials using β-blockers for daily-life ischaemia.

In four reports using propranolol, a total of 153 patients were studied[27–30]. The mean daily dose of propranolol was just above 300 mg. Overall, there was about a 60% reduction in the number and duration of ischaemic episodes. In two studies with metoprolol, the mean daily dose was 400 mg and the reduction in the number and duration of ischaemic episodes was about 80%[31,32]. Compared with propranolol (313 mg mean), the metoprolol dose was larger (400 mg mean) and the number of patients was relatively small 19 metoprolol vs 153 propranolol.

In five studies with atenolol, a total of 72 patients were reviewed and the average daily dose of atenolol was just over 100 mg[33–37]. Treatment was associated with a reduction of about 64% in the number and a reduction of about 78% in the duration of ischaemic episodes. This dose is lower than either the metoprolol or propranolol doses. The results of these studies of β-blockers were fairly consistent so the results of over 200 patients were combined. Average reductions in the number and duration of ischaemic episodes were in the 60–80% range. There is also a dose–response relationship; the studies which used larger doses showed a greater decrease in daily-life ischaemia.

CALCIUM ANTAGONISTS

In 11 controlled studies of the calcium antagonist, nifedipine, which included 301 patients, the mean daily dose of nifedipine was 64 mg[27,28,35,38–45]. The average reduction in the number of ischaemic episodes was 39% and the average reduction in the duration of the episodes was 43%, and there was no clear dose–response relationship.

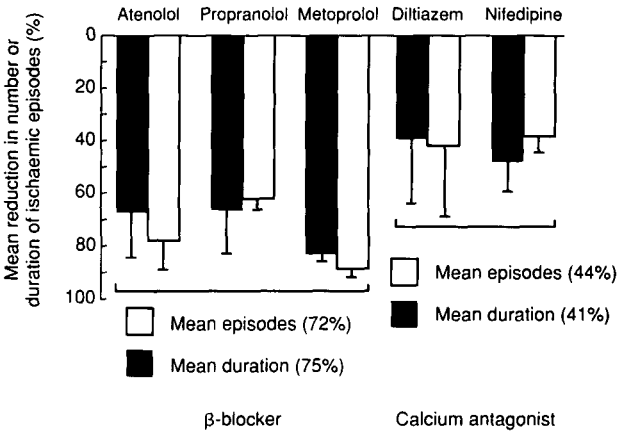

Figure 3 Comparison of β-blockers and calcium antagonists in the reduction in daily-life ischaemia.

In five studies of the heart rate-specific calcium antagonist, diltiazem[27,30,37,41,46], a total of 149 patients received a mean daily dose of 320 mg. There was a 48% reduction in the number and a reduction in the duration of ischaemic episodes.

Experience with verapamil was limited to data from only one small controlled trial[40].

COMBINED RESULTS

The combined results of the β-blocker and calcium antagonist trials are summarized in Fig. 3. In the β-blocker trials there was an average reduction of about 70% in both the duration and number of ischaemic episodes, while in the calcium antagonist trials there was an average reduction of about 40%. These data suggest, therefore, that β-blockers prevent a greater proportion of daily-life ischaemic episodes than calcium antagonists.

One recently published study[27] on calcium antagonists and β-blockers compared the effect of placebo, diltiazem, propranolol, and nifedipine in the same 50 patients. The β-blocker eliminated the morning increase in heart rate and reduced the rise in ischaemic episodes that began in the morning hours. Nifedipine exaggerated the morning increase in heart rate and it remained elevated throughout the day. The response to diltiazem was intermediate between propranolol and nifedipine. Thus, calcium antagonists did not reduce daily-life ischaemia as much as β-blockers.

Several other recent studies compared responses to calcium antagonists and β-blockers in the same patients. In studies by Deedwania *et al.*[38] and Hill *et al.*[35], atenolol and nifedipine were compared. In another study by Raymenants *et al.*[37], atenolol and diltiazem were compared. Analysis of these data revealed a highly significant reduction in the incidence of daily-life ischaemia of about

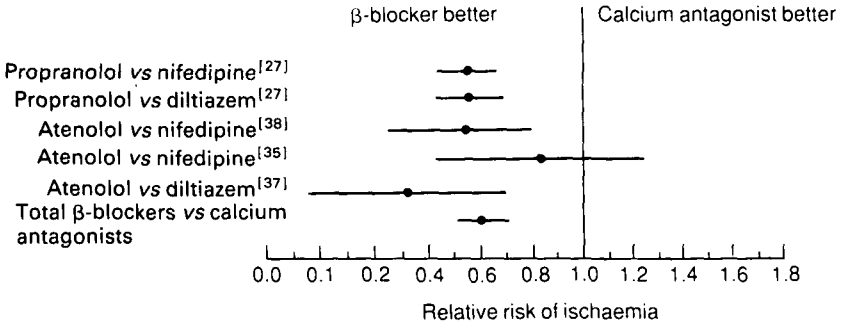

Figure 4 Comparison of β-blockers and calcium antagonists in patients with daily-life ischaemia and stable angina. Values are relative risk of ischaemia and 95% confidence intervals.

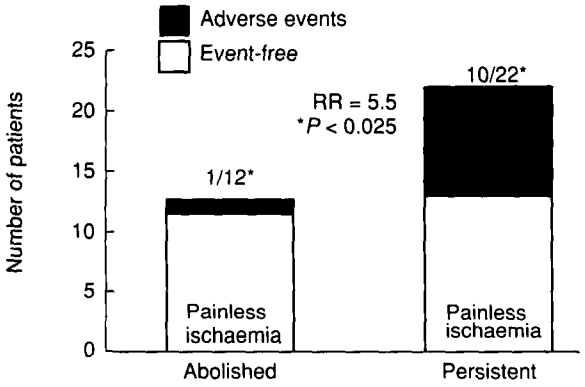

Figure 5 The association of adverse events and persistent painless ischaemia. Painless ischaemia was abolished by medical therapy in 12 patients and persistent in 22 patients. At follow up persistent painless ischaemia was associated with a relative risk (RR) of adverse events of 5·5. Adapted from Lim *et al.*[51].

40% by β-blockers compared with calcium antagonists (Fig. 4). Thus, these data suggest that the relative risk for daily-life ischaemia is considerably less during treatment with a β-blocker compared with a calcium antagonist.

There are additional advantages to β-blocker therapy. Numerous epidemiological studies indicate that a low heart rate is beneficial in patients with ischaemic heart disease[47,48]. Other studies in animals suggest that low heart rate is associated with less severe experimental coronary atherosclerosis[49,50]. Most myocardial infarctions and episodes of ventricular tachycardia and ventricular fibrillation which do not take place in hospital, occur in the morning. They are reduced by β-blockers. β-blocker activity coincides with ischaemic episodes and related adverse events making them the most likely candidates to influence outcome.

Unanswered questions

There are no controlled trial data to prove that treating patients for daily-life ischaemia improves outcome, nor that suppression of ischaemia is associated with benefits. In a recent pilot-type study, however, Lim *et al.*[51] described a small group of patients who had painless exercise-induced ischaemia-related left ventricular wall motion abnormalities. After 4 weeks of anti-ischaemic pharmacotherapy, the patients were divided into two groups based on another exercise wall motion (e.g. radionuclide ventriculogram) study. In one group, treatment abolished painless ischaemia, while in the other group, painless ischaemia persisted despite therapy. After 9 months of follow-up, all but one of the adverse events that occurred were in the group of patients in whom painless ischaemia persisted (Fig. 5). Although this was a small study of short duration (only 34 patients with a brief, 9-month follow-up) the results support the hypothesis that abolition of painless ischaemia is associated with reduction of adverse outcome.

Trials in progress

There are five controlled trials currently underway or recently completed (Table 3): Total Ischaemic Burden European Trial (TIBET), Canadian Amlodipine Silent Ischaemia Study (CASIS), Atenolol Silent Ischaemia Trial (ASIST), Asymptomatic Cardiology Ischaemia Pilot (ACIP), and Angina Prognosis Study in Stockholm (APSIS).

In TIBET over 600 patients were enrolled, but only about one-third of the patients had daily-life ischaemia. Three treatment strategies were examined; atenolol monotherapy, nifedipine monotherapy, and atenolol–nifedipine as combination therapy. The primary outcome data will be published in the near future[52].

In CASIS, 120 patients were randomized to either amlodipine, atenolol, or a combination of these agents. This study had a follow-up period of only 9 weeks and the primary end-point was suppression of ischaemia. These results will also be published in the near future.

In ASIST, the target sample size is 350 asymptomatic or minimally symptomatic patients with evidence of CAD and abnormal exercise tests who also have silent daily-life ischaemia. The patients are randomized to receive either atenolol or placebo and will be followed for 1 year. Adverse outcome is the primary end-point. This study has enrolled about 90% of patients needed and results should be available in late 1993.

Table 3 Ongoing trials to access therapy for daily-life ischaemia and outcome

Trial/contact	Target number	Assessment period	Treatment
CASIS/R. Davis Ottawa	120	3 months	Amlodipine vs atenolol vs combination
ASIST/C.J. Pepine Gainesville	350	1 year	Placebo vs atenolol
TIBET/K. Fox London	600	3 years	Atenolol vs nifedipine vs combination
ACIP/G. Sopko Bethesda	600	1 year	Symptom-guided care vs ischaemia-guided care vs revascularization
APSIS/P. Hjemdahl Stockholm	790	15 months	Verapamil vs metoprolol

CASIS = Canadian Amlodipine Silent Ischemia Study
ASIST = Atenolol Silent Ischaemia Trial
TIBET = Total Ischaemic Burden European Trial
ACIP = Asymptomatic Cardiac Ischaemia Pilot
APSIS = Angina Prognosis Study In Stockholm

In the Swedish trial, APSIS, 790 patients are enrolled and randomized to either metoprolol or verapamil. The end-point is adverse outcome over 15 months.

ACIP has been initiated. A total of 618 patients with CAD, abnormal exercise test response, and silent daily-life ischaemia are randomized to one of the three treatment strategies: angina-guided therapy, angina plus ischaemia-guided therapy, and revascularization (e.g. percutaneous transluminal coronary angioplasty or coronary artery bypass graft). Within the two medical treatment strategies, patients are also randomized to receive a dose-titrated regimen of either atenolol plus nifedipine or diltiazem plus isosorbide dinitrate, and will be followed for 1 year which will end in December 1993. This study is a pilot study for a major trial: the Asymptomatic Cardiac Ischaemia Project (ACIP-II). This full scale trial would involve 5000 patients and would examine the effect of ischaemia treatment on mortality. The major trial could begin as early as 1994 and could include centres in the U.S.A., Canada, and Europe.

β-BLOCKERS AND CALCIUM ANTAGONISTS IN COMBINATION

Some data suggest that there are advantages to the combination of β-blockers and calcium antagonists. The pathophysiology of daily-life ischaemia includes both increases in myocardial oxygen demand and limitations and reductions in myocardial supply. Therefore, a combination of β-blockers, which reduce myocardial oxygen demand, and calcium antagonists, which improve myocardial oxygen supply, should theoretically be advantageous. Dargie *et al.*[28] examined the effects of combining propranolol and nifedipine. This combination yielded a greater reduction in daily-life ischaemic episodes than either agent used as monotherapy. Hill *et al.*[35] and Raymenants *et al.*[37] used combinations of atenolol plus nifedipine and atenolol plus diltiazem; once again, the combination appeared to be superior to monotherapy. Likewise, in the study by Parmley *et al.*[44] the combination of long-acting nifedipine with a β-blocker provided superior reduction in the number and duration of ischaemic episodes. An additional advantage to combination therapy is that the doses can be reduced leading to a reduction in side-effects.

Summary

Daily-life ischaemia, most of which is silent, has been associated with increased risk for adverse outcome. β-blockers, which reduce heart rate and blood pressure and have other important effects, also reduce or eliminate daily-life ischaemia. Data from the published literature indicate that β-blocker therapy has a greater effect than calcium antagonists in the suppression of daily-life ischaemia when these agents are used as monotherapy. Combination therapy with a β-blocker and a calcium antagonist appears to have distinct advantages over monotherapy. Definitive data showing that treatment of patients with daily-life ischaemia reduces adverse outcome are lacking. Likewise, direct evidence supporting the hypothesis that suppression of ischaemia is associated with reduction in adverse outcome awaits the results of large-scale clinical trials. There should be considerable new information on this important problem in the next few years.

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